59. The DNA segment of claim 59 comprised within recombinant herpes simplex virus vector d27.1.

60. A kit comprising the DNA segment of claim 58 and directions for use.

REMARKS

Status of the Claims

Claims 1-27 have been canceled without prejudice and without disclaimer.

Claims 41-60 have been added.

Claims 41-60 are pending in the case.

Oath/Declaration

The Declaration of Barry Byrne is stated to be defective for failure to indicate citizenship of the Declarant. A substitute Declaration accompanies this response.

Misnumbered Claims

Applicants take notice that the Examiner has corrected the misnumbering of the claims. Applicants have numbered the added claims in accordance with the correction, presumably entered by the Examiner; accordingly, the added claims begin with "41" rather than "40".

Rejection of Claim 6 Under 37 C.F.R. §1.75

Claim 6 has been objected to as a substantial duplicate of claim 4 and therefore afoul of 37 C.F.R. §1.75 for double patenting.

Applicants respectfully submit that the substitute added claims distinguish the claimed recombinant HSV vectors and related DNA segments. For example, claims 46 and 50 are distinguishable as a mutant virus (46) and recombinant vector (50). Accordingly, it is believed that the rejection under 37 C.F.R. §1.75 is moot.

Rejection of Claims 19, 23 and 27 under 35 U.S.C. §112, First Paragraph

Claims 19, 23 and 27 have been rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for not describing the subject matter in such a way as to enable one skilled in the art to make and use the invention. The Action is of the opinion that the recombinant HSV described as d27.1 rc HSV-1 is not sufficiently described to allow one to reproducibly construct the material from available starting materials and methods either known or described.

Applicants believe that d27.1.rc HSV-1 is amply described in the specification. By way of clarification, virus d27.1 is an intermediate early deletion mutant of the ICP27 gene encoding an immediate early protein of HSV-1. The preparation of virus d27.1 is detailed in Section 9.1.3 on page 64 of the specification.

Additional description is found in FIG. 2 which shows the integration vector used to produce d27.1-rc by homologous recombination. The recombinant vector, also referred to as rHSV-1, d27.1-rc, is a homologous recombination of AAV-2 *rep* and *cap* genes into the *tk* locus of the rHSV-1 virus d27.1 (see FIG. 2 and section 9.2.1). It should be noted that vector HSV-RC/d27 has also been termed d27.1rc (please refer to section 4.0, line 15, page 12 in the

specification). This vector includes the AAV *rep* and *cap* genes under control of their respective native promoters so that rescue and replication of rAAV genomes are possible when the recombinant vector is used to supply *rep* and *cap*.

The specification therefore contains adequate written description sufficient to be enabling because a reproducible method is set forth in the specification with sufficient description of reagents and materials for one skilled in the art to reproduce the claimed herpes simplex mutant, vectors and DNA constructs.

Rejection of Claims 9-10 and 20-27 under 35 U.S.C. §112, Second Paragraph

Claims 9-10 and 20-27 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The term "altered to increase expression" in claim 9; the term "suitable container" in claims 20 and 24; and the antecedent basis for "said HSV-1 helper virus" are believed not to be relevant considerations in the added substitute set of claims (41-60).

Rejection of Claims 1-8, 11, 12, 15-18, 20-22 and 24-26 Under 35 U.S.C. §102(b)

Claims 1-8, 11-12, 15-18, 20-22, and 24-26 have been rejected under 35 U.S.C. §102(b) as anticipated by Dong *et al.* The Action cites Dong *et al.* as describing helper viruses that may be prepared from AV or HSV which are either replication competent or replication defective, the former comprising viral packaging and origin of replication sequences. The Action further notes that, in general, Dong *et al.* describe HSV helper viruses that include "...one or more of the AAV *rep, lip* and *cap* genes (page 7, lines 8-20)", see page 7, line 1 of the Official Action.

Applicants draw attention to the construct of claim 1 which is a DNA segment engineered to contain the AAV *rep* and *cap* genes with their promoters, an HSV-1 origin of replication and an HSV packaging sequence. The herpes virus vectors described by Dong *et al.* are recombinants that have AAV *rep*, *lip* and/or *cap* HSV-1 inserts (page 7, lines 9-10) rather than the constructs engineered from the segments included in claim 1. Moreover, while Dong *et al.* globally speak of inserted expression regions comprising one or more *rep*, *lip* and *cap* genes, there is neither claim nor description of a herpes virus vector engineered specifically with *rep* and *cap* genes. Applicants have more particularly described the DNA segment in added substitute claim 58 and in the HSV mutant virus claims 41 and 46 and the vector claim 50, as well as the claims dependent thereon.

Each and every element of a claim must be set forth in a prior art reference in order for the Action to show anticipation or at least be "substantially identical" to what is disclosed in the prior art. Thus anticipation is established only when a single prior art reference explicitly or inherently discloses each and every element of the claimed invention, RCA Corp. v. Applied Digital Data Sys., Inc., 221 U.S.P.Q. 385, 388.

Applicants submit that Dong *et al.* do not explicitly set forth the elements of claims 1-8, 11-12, 15-18, 20-22 or 24-26 as discussed and particularly not in the added substitute claims. Nor does the reference inherently disclose applicants' constructs. The reference merely mentions that HSV may be used to construct helper virus by insertion of some number of AAV genes required for replication into the HSV genome. Much discussion in the reference ensues on how one might approach obtaining various helper AV or HSV virus vectors, but other than stating that one or more of *rep*, *lip* or *cap* genes could be inserted into any of several herpes viruses, the reference does not disclose applicants' DNA segment.

Regarding claim 16, the reference nowhere explicitly discusses a *rep*, *cap*, recombinant herpes simplex virus. A reading of the reference as a whole at best provides only an "inherent" suggestion to supply the Rep, Lip and/or Cap proteins to cells by inserting *rep*, *lip* or *cap* into a herpes virus.

Applicants therefore respectfully request withdrawal of the Action's anticipation rejection based on Dong, *et al.*.

Rejection of Claims 1-8, 11, 12, 15-17, 20-22 and 24-26 Under 35 U.S.C. §103(a)

Claims 1-8, 11-12, 15-17, 20-22 and 24-26 have been rejected under 35 U.S.C. §103(a) as unpatentable over Dong *et al.* in view of Chiorini *et al.* The action cites the Chiorini *et al.* reference as disclosing a two vector system, one of which is an rAAV vector and the second a vector that includes the *cap* and *rep* AAV genes, an inducible origin of replication and a suitable promoter such as p5, p19 and p40 from AAV. The Action takes the position that one could construct the helper HSV vectors mentioned in Dong *et al.* and use the promoters listed by Chiorini *et al.* in view of Dong *et al.*'s statement that one could use any heterologous or wild type promoter to cause expression of "essential" genes, which applicants assume the Action means to be the *rep*, *lip* and *cap* genes.

Even if Dong *et al.* had explicitly named the p5, p19 and p40 promoters as suitable to drive the *rep*, *lip* and *cap* genes, applicants do not believe such information renders the claims obvious. Dong *et al.*'s teaching is directed to the insertion of the *rep*, *lip* and *cap* genes into the AV or HSV genome without much consideration for modifications other than replacing a gene required (or not) for HSV replication with one of the AAV "essential" genes. However, applicants fail to see that Chiorini *et al.*'s explicit mention of the AAV promoters in any way

suggests the claimed construct of claim 1 which is defined as having the *rep* and *cap* genes with promoters, an HSV origin of replication and an HSV packaging cassette. The general construct is further defined in added substitute claims 41, 46, 50 and 58.

The Action has placed a high amount of reliance on the Dong *et al.* reference. Applicants respectfully direct attention to the entire reference and what one of skill in the art may reasonably accept as its teaching.

Dong *et al.* reviews generally what is known in the art regarding vector construction, and asserts that one may make vectors from AV and HSV, insert genes from AAV into the AV or HSV genome, or delete some of the genes from AV or HSV when making the inserts. The reference also notes that one should put promoters in the vectors to express the AAV genes, and, finally, that the inserted genes should be the AAV genes required for AAV replication, *i.e.*, *cap*, *lip* and *rep*.

What the Dong *et al.* reference actually describes are AAV inserts into the E3 region of AV, such as *Adrep*3, *Adcap*3 and *Adrc*3. These constructs include the *rep-lip* gene, the *cap* gene or the entire *rep-lip-cap* gene (page 9, lines 15-21). Nowhere is a construct of *rep-cap* claimed, nor is one disclosed.

It would appear, therefore, that one of skill in the art would not be motivated to make an HSV expression vector with a *rep-cap* insert because the discussion, the experiments and the claims noticeably omit such a combination; instead, the ordinary skilled artisan would be led to use the particularly described constructs.

As for Chiorini *et al.*, the mere revelation that one could link an AAV promoter with an AAV gene does not provide motivation to engineer applicants' constructs.

Rejection of Claims 1-8, 11, 12, 15-18, 20-22 and 24-26 Under 35 U.S.C. §103(a)

Claims 1-8, 11-12, 15-18, 20-22 and 24-26 have been rejected under 35 U.S.C. §103(a) as unpatentable over Dong *et al.* and Glorioso *et al.* Glorioso *et al.* is cited for discussing several HSV vectors, including the proposition that it is possible to make deletion mutations in certain HSV genes in order to make the virus replication defective. The Action takes the position that the Glorioso *et al.* reference provides information to modify the Dong *et al.* vectors by deleting at least part of the ICP27 gene because the skilled artisan knows how to make the deletions. The Action further provides its own motivation by stating that it would have been obvious to experiment and modify the HSV constructs by making non-essential or essential deletions of genes such as glycoprotein H or ICP27 and that motivation is found because Glorioso *et al.* say that it is desirable to make such modifications. The Action appears to find both motivation and expectation of success in the combination of references. Applicants respectfully disagree that there is neither motivation nor expectation of success.

Applicants traverse the Action's rejections based on obviousness in view of the cited references. Motivation to experiment with deletions, deletions of different genes in HSV or with different constructs was a challenge to Applicants to improve *rep* and *cap* inducible cell lines because current procedures utilizing *rep* and *cap* plasmids had a tendency to generate wild-type AAV (see page 5 of the specification). The problem to be solved was to develop a packaging system that provided all the helper functions required for rAAV production from rAAV producer cell lines and thus allow large scale production of rAAV. Despite knowledge of the genes involved, procedures for constructing expression vectors, and gene modification techniques,

others had not disclosed the recombinant AAV vectors that provided high titer rAAV production.

Added claims

In order to more clearly define the invention, Applicants have provided a new set of claims (Exhibit "A") directed to novel recombinant vectors, amplicons and kits. The new claims are directed to the same invention but are believed to more clearly distinguish the constructs from other vectors that have been proposed and to better describe particular constructs set forth in the specification.

The following is a table indicating the relationship of the added claims to the claims currently under examination and, where appropriate, the support in the specification for particular features in dependent claims.

Added Claims	Pending Claims
41	16, 19 (see Specification, p. 12, lines 15, 20)
42	17
43	Specification, page 9, line 30; page 14, line 13)
44	Specification, page 9, line 25
45	Specification, page 9, line 25
46	15, 19 (in part)
47	9 (in part)
48-49	13
50	10 (in part)
51	13, 14
52	Specification, page 9, line 25
53	Specification, page 9, line 25
54	2, 6
55	3, 6
56	24-27
57	
58	1 and Specification, page 16, lines 13-14
59	19
60	20, 22-23

Applicants intend this to be a complete response to the examiner's action and respectfully request reconsideration of the application. The response is directed at the pending claims which is urged to be considered in light of the added replacement claims that are believed to more clearly characterize the invention and to overcome any objections raised by the examiner to the canceled claims.

The Examiner is invited to contact the undersigned attorney at 713.934.4091 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Barbara S. Kitchell

Barbara S. Kitchell
Reg. No. 33,928

Attorney for Applicants

WILLIAMS, MORGAN & AMERSON
7676 Hillmont, Suite 250
Houston, Texas 77040
(713) 934-7000

Date: September 28, 2000